The immunological regulation of cancer cachexia and its therapeutic implications

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Abstract
Cachexia affects the majority of patients with advanced cancer. It leads to poor surgical and oncological outcomes, and negatively affects quality of life. It has long been reported that components of the host immune system, including pro-inflammatory cytokines such as IL-1α, IL-6, TNF-α and INF-γ, participate in the syndrome of cachexia. Yet therapeutic targeting of these pro-inflammatory factors has not yielded meaningful improvements in cachexia management. More recently, the impact of immune cells in the tumour mass (tumour-associated macrophages) and host circulation (myeloid suppressor cells) has garnered much interest with regards to their role in immune tolerance in cancer. However, their role in the generation of systemic inflammation and cancer cachexia is underexplored and outstanding questions remain. This review summarises the key mediators and targets of immune dysfunction in cancer cachexia. Here we describe the host response including skeletal muscle wasting; highlight the current knowledge gap areas; and report the results of previously trialled immunotherapies. A greater understanding of complex interaction between the tumour, immune system and peripheral tissues in the genesis and maintenance of cancer cachexia is a key step in identifying future therapeutic targets.

Keywords: Cancer cachexia, interleukins, macrophages, immunotherapy

INTRODUCTION
Cachexia is “a multifactorial syndrome defined by an ongoing loss of skeletal muscle mass (with or without loss of fat mass) that cannot be fully reversed by conventional nutritional support and leads to progressive
functional impairment"[1]. Cachexia has a negative impact on a large proportion of patients with advanced cancer with it contributing to high levels of morbidity and mortality[2]. Although there still remains some debate over the formal definition of cancer cachexia, it is characterized by unintentional weight loss, muscle wasting, anorexia and fatigue[3]. Systemic inflammation is a key driver of cancer cachexia and has been advocated as a core nutritional assessment in patients with cancer[4,5]. Pro-inflammatory cytokines are activated by the tumour mass, and act both centrally (through anorexia) and peripherally (by skeletal muscle wasting) to result in host nutritional depletion[6]. Tumour and host-derived factors thus lead to a chronic inflammatory and impaired immune state[7]. Immunosuppression is a large problem in cachectic cancer patients contributing to reduced responses to surgical and oncological outcomes[8]. The dysfunction of the immune system is complex and involves multiple mechanisms characterised by a reduction in monocyte, macrophage, dendritic and natural killer (NK) cell function, ultimately leading to susceptibility to infections, and therefore, an overall increase in morbidity[9].

In short, it has long been apparent that systemic inflammation plays a role in the pathogenesis of cancer cachexia. The successful therapeutic targeting of systemic inflammation requires a better understanding of the involved mediators and the link between tumour and immune tissues. This review aims to describe some of the key elements of immune dysfunction in cachexia and give an overview of previously trialled immunotherapies.

PRO-CACHECTIC CYTOKINES

TNF-α

TNF-α (previously known as “cachectin”[10]) was initially held responsible for causing most of the metabolic derangements and clinical features of cachexia. TNF-α is released by many types of cell, including activated macrophages, CD4+, neutrophils, mast cells, eosinophils and neurons. In particular, it can be produced by tumour, immune and stromal cells to induce growth and survival advantage in the tumour microenvironment[11]. Its expression can ultimately lead to anorexia, muscle and adipose wasting, loss of appetite, increased energy expenditure and insulin resistance in both patients with various types of cancer, and the Colon-26 carcinoma mouse model of cancer cachexia (C26)[12]. Many of the effects of TNF-α arise through activation of NFκB, which in turn leads to activation of the ubiquitin-proteasome pathway and skeletal muscle degradation[13]. It also acts to induce oxidative stress and nitric oxide species (NOS). Experimental evidence suggests TNF-α can induce adipose wasting in white adipose tissue through inhibition of lipoprotein lipase (LPL), suppression of transcription and promotion of lipolysis[14,15] as well as stimulation of thermogenesis through increased expression of UCP2 and UCP3 in skeletal muscle.

The role of TNF-α in mediating many of the effects of cancer cachexia was initially supported by evidence that intraperitoneal injection of soluble recombinant human TNF-receptor antagonist was able to improve food intake and thus lead to weight gain in tumour-bearing rats[16]. Lewis lung carcinoma (LLC) mice deficient in TNF-α receptor protein type 1 showed a reduction in muscle wasting compared with LLC wild-type mice despite similar levels of TNF-α being detected in the serum[17]. Treatment with antioxidants or NOS inhibitors was shown to increase body weight and prevent muscle wasting in mice[18]. Despite this, TNF inhibition alone in animals has not been shown to be sufficient to reduce or reverse the cachectic process indicating that, although it is involved in the pathogenesis of cancer cachexia, it is not solely responsible[19].

Studies in patients with cancer, have also not been successful. In particular adipocytes taken from cancer patients, showed no decrease in LPL messenger RNA (mRNA) or LPL enzyme activity[20]. Some studies have shown raised TNF-α levels in the serum of patients with pancreatic cancer associated with weight loss, whereas other studies in patients with terminal cancer showed no association between TNF-α and weight loss[21,22]. Others have shown that TNF-α correlates with stage of disease or tumour size rather than degree
of weight loss. These discrepancies between studies may be due to differences in measuring techniques, possible auto or paracrine roles for TNF-α in adipose tissue, or heterogeneity between patients, sexes and tumours.

In summary, TNF-α is involved in systemic inflammation, but as cachexia is likely to be multifactorial, it is difficult to implicate TNF-α as the sole cause. More clinical studies are required to fully isolate its effects in patients.

**Interferon gamma**

Interferons are multifunctional cytokines that block viral infections and affect cell proliferation and differentiation. Interferon gamma (IFNγ) is produced by activated T and NK cells, and is arguably the most potent monocyte-macrophage activating factor. In the context of cancer, tumour-infiltrating lymphocytes (TILs), which have shown to be of particular importance in tumour immunosurveillance, are the main source of IFNγ. There is an overwhelming body of evidence for both beneficial and detrimental roles of IFNγ in a range of diseases, including cancer. However, its role in patients with cachexia is a relatively underexplored area.

Several animal studies have indicated a central role for IFNγ in the pathogenesis of cachexia. Central administration of rat interferon resulted in decreased food intake whereas peripheral administration failed to do so. Mice overexpressing IFNγ producing tumour cells developed loss of body weight, atrophy of adipose tissue, and reduced appetite, all of which were then reversed by pre-treatment of the mice with anti-IFNγ antibodies. Mice with LLC also demonstrated a reduction in weight loss after treatment with anti-IFNγ antibody, significantly reducing fat wasting in particular. In rats that had received transplants of MCG 101 sarcoma, anti-IFNγ antibody reduced weight loss, but the effect of treatment was short-lived. Similarly to TNF-α, IFNγ has been shown to inhibit LPL activity in adipocyte cells in vitro, as well as that of glycerol phosphate dehydrogenase in cultures of rat adipocytes.

**IL-1α**

Levels of IL-1α have been shown to be increased in animal models of cachexia. It is thought to cause similar effects to that of TNF-α. IL-1α is a pro-inflammatory cytokine produced mainly by macrophages and endothelial cells and is known for being a trigger of the acute phase response, thus playing a role in cancer pathogenesis, as well as shock and autoimmune disorders. In a similar fashion to other cytokines discussed, it is also able to inhibit LPL activity and stimulate lipolysis in cultured adipocytes. The ability of IL-1 to induce anorexia is thought to be due to a central effect on appetite suppression involving blockade of neuropeptide Y. It also increases plasma concentrations of tryptophan and serotonin leading to early satiety and suppression of hunger.

Again, there is evidence for the role of IL-1α in animal models of cachexia, but little in humans. IL-1α can induce cachexia and anorexia in rats. IL-1α treated rats showed loss of body weight. Administration of IL-1α receptor antagonist (IL-1ra) to tumourbearing rats however, did not result in any improvement in body weight. Following direct tumour injection with IL-1ra, C26 mice demonstrated significantly reduced weight loss (without an effect on tumour burden) compared with mice who had systemic injection. Cultures of C26 cells also demonstrated raised levels of IL-6 after stimulation with IL-1α, which were suppressed by monoclonal antibody to IL-6. In tumour samples from patients undergoing surgical resection for upper gastrointestinal malignancy, IL-1β and IL-6 were also significantly overexpressed in the cancer specimens, at both mRNA and protein levels, compared with control mucosa. Protein levels were seen to correlate with CRP, indicating that tumour may be the source of IL-1β.
IL-1β
IL-1β is a proinflammatory cytokine released by macrophages. It regulates the expression of other cytokines including IL-6 and IL-12. Recently, the loss of p53 in cancer cells from breast cancer mouse models have been shown to induce the secretion of WNT ligands that stimulate tumour associated macrophages (TAMs) to produce IL-1β, therefore helping to drive systemic inflammation. Macrophages were prevented from secreting IL-1β by pharmacological and genetic blockade of WNT secretion in p53 null cancer cells. This blockade also resulted in decreased neutrophilic inflammation and metastasis formation [40]. These findings therefore suggest an important potential future role for personalised immune therapy in patients with cancer cachexia.

IL-1β has also been better associated with the clinical features of cachexia such as anorexia, weight loss and sarcopenia than other cytokines such as IL-6 in a study of 83 advanced cancer patients [41]. Patients with gastric cancer cachexia have also been shown to have a higher prevalence of IL-1B+3954 T allele than those without indicating that patient genotype plays a role on immunological regulation of cancer cachexia [42].

IL-6
IL-6 can target adipose tissue, skeletal muscle, gut, and liver tissue, which can all affect cachectic patient body composition. It signals through the membrane bound receptor gp130 found in most tissues in the body [43]. Once bound to its receptor, it activates JAK tyrosine kinase leading to phosphorylation of tyrosines and the binding of STAT proteins. STAT proteins can translocate to the nucleus and increase the transcription of genes involved in immune function, cell proliferation, differentiation and apoptosis [43].

Several mouse cancer models have clearly demonstrated that blocking IL-6 and associated signalling can attenuate cachexia progression. Deletion of the IL-6 gene in the APCMin/+ mouse prevented the development of cachexia [44]. IL-6 when secreted by tumour cells can also increase autophagy in myotubes when joined with soluble IL-6 receptor [45]. IL-6 trans-signalling through the soluble IL-6R has the potential to amplify IL-6 signalling in the cachectic patient and has been shown to be involved in cross-talk between tumour, muscle and adipose tissue in genetic mouse models of pancreatic cancer cachexia [46]. Autophagy and increasing IL-6 levels have been associated with poor prognosis and weight loss in lung cancer patients [45]. It has also been shown to be the key cytokine that regulates the hepatic acute phase response in patients with pancreatic cancer cachexia [47]. IL-6 remains a promising therapeutic target in cancer cachexia but a better understanding of its direct and indirect effects, as well as tissue specific actions, is required.

CYTOKINE GENOTYPE
The presence and concentration of (potentially) pro-cachectic cytokines in cancer patients appear to be dependent not only on the type of tumour, but also on the burden of disease present, and patient specific factors such as age, sex and genotype. It is still not fully understood why patients with the same histological disease may vary with regards to the presence and severity of cachexia. Genetic variation in immunity is one possible reason. Specific single nucleotide polymorphisms in the IL-1, IL-6 and IL-10 genes have been associated with cachexia in gastrointestinal cancers [48]. The 1082G allele in the IL-10 promoter was validated in an independent cohort. This was shown to be more prevalent in Myc/mTOR-driven mouse models of cachexia as well as cachectic colorectal cancer patients [48]. The C allele of the rs6136 polymorphism in the P-selectin gene has also been associated with weight loss and low CT muscularity in a large group of cancer patients [49]. These results suggest a role for the immune system in the complex presentation of cachexia.

CELLS
Myeloid derived suppressor cells
Many studies have now suggested that tumour infiltrating immune cells (those which are mainly of myeloid origin) are able to differentiate into cells which then promote tumour growth and metastasis
through their ability to induce systemic inflammation\(^\text{[50]}\). Tumours can grow through myelopoiesis and the successful evasion of tumour cells from both the innate and adaptive immune systems\(^\text{[51]}\). However, the progression of cancers appears dependent on tumour-associated myeloid cells through their ability to promote angiogenesis and tissue remodelling\(^\text{[52]}\). This apparent immunosuppression has been linked to the development of cachexia in very few studies, despite tumour-induced immunosuppression being well documented in the literature\(^\text{[53]}\).

Myeloid derived suppressor cells (MDSC) may play a role in tumour-related immunosuppression. Tumour-induced amplification of the myeloid compartment leads to the expansion of myeloid-derived suppressor cells. MDSC’s are immature myeloid cells in various stages of differentiation, but are not fully differentiated neutrophils, monocytes/macrophages or dendritic cells. They are found in the bone marrow, spleen, lymph nodes and tumours\(^\text{[50]}\). Their mechanisms of action are not fully understood but they are thought to be immunosuppressive and to play a role in the over production of cytokines and inflammatory mediators, which may contribute to cachexia.

MDSC expansion in 4T1 breast carcinoma-bearing mice is associated with the induction of the hepatic acute phase protein response and altered fat metabolism\(^\text{[53]}\). This response is also seen in the C26 and LLC mouse models. The pro-cachectic acute phase response is not seen, however, in 66C4 subclone of 4T1 mice in which MDSC expansion does not occur\(^\text{[53]}\). Defects in myeloid cell-mediated inflammation has also been shown to result in reduced expression of pro-inflammatory cytokines in the serum of mice with hepatocellular carcinoma\(^\text{[54]}\). Interestingly, this led to enhanced loss of adipose tissue and decreased macrophage number in visceral adipose tissue, suggesting a possible local role for macrophages in the regulation of cancer-induced fat loss\(^\text{[54]}\). These findings imply that myeloid cell-mediated inflammation confers a beneficial function in these rodents, and may provide a potential explanation for the failure of several anti-inflammatory drugs in treating cachexia. Although a direct link between the development of cachexia and MDSC’s has not been proven, the above studies have suggested that the development of cancer cachexia is partly explained by the expansion of immature myeloid populations associated with the tumour.

**TAMs**

TAMs increase tumour progression and metastasis and suppress anti-tumour immune functions\(^\text{[55]}\). Monocytes from blood infiltrate the tumour and are primed by the tumour microenvironment to exert these effects\(^\text{[56]}\). The immune cells within the tumour’s microenvironment consist of myeloid-derived suppressor cells, NK cells, dendritic cells, T cells and macrophages\(^\text{[56]}\). It is this infiltrate that contributes to tumour growth and the release of cytokines that promote the pro-cachectic environment. TAMs are recruited via cytokines and chemokines and suppress the activity of cytotoxic T-lymphocytes via programmed cell death 1 ligand 1 (PD-L1) or B7-H4 and other receptors\(^\text{[57]}\). Activated macrophages also secrete cytokines leading to the activation of several complex cascades, thereby increasing inflammatory status\(^\text{[58]}\). The chemokine monocyte chemotactic protein-1 is possibly responsible for the migration of monocytes to adipose tissue in chronic inflammation\(^\text{[59]}\). The mechanisms by which macrophages modulate adipocyte function in cachexia are still unclear.

**TILs**

TILs are often found in tumours and are thought to reflect an immune response against the tumour. Many studies report a survival benefit associated with the presence of TIL, suggesting they may delay tumour progression. CD3+ and CD8+ TILs in particular have been identified as having a positive effect on prognosis\(^\text{[60]}\).

**IMMUNE SYSTEM BIOMARKERS**

The Neutrophil: Lymphocyte ratio is a prognostic indicator in cancer. Neutrophils increase the inflammatory reaction to pathogens but also interact with cancer cells to produce cytokines and effector
molecules (e.g., VEGF) that are able to stimulate angiogenesis and promote tumour growth.\(^{[41]}\) Activated neutrophils can move from the circulation to the tumour site to release reactive oxygen species that in turn can lead to further DNA damage. They also have anti-tumour roles through antibody-mediated cytotoxicity of tumour cells.\(^{[42]}\)

C-reactive protein is an acute phase non-specific inflammatory marker that can be elevated in response to infection, surgery or malignancy. It is produced by the liver in response to increased levels of IL-6 released by activated macrophages, as well as IL-1 and TNF-\(\alpha\).\(^{[43]}\) The Glasgow Prognostic Score utilises raised CRP and hypalbuminaemia to predict those patients with systemic inflammation as part of cancer cachexia and who have a poor outcome. It has been examined in more than 60,000 patients and has been shown to have independent prognostic value.\(^{[44]}\)

**IMMUNOTHERAPEUTIC AGENTS FOR CANCER CACHEXIA**

Immunotherapeutic agents for cancer cachexia have yielded mixed results. The different forms of immunotherapy are discussed in detail below.

**TNF-\(\alpha\) inhibitors**

There are currently several TNF inhibitors in use for the management of diseases such as rheumatoid arthritis (RA), psoriasis and inflammatory bowel disease, namely etanercept, infliximab and adalimumab.\(^{[45]}\) These drugs have revolutionised the treatment of RA but have also offered insights into the role that TNF-\(\alpha\) plays in cachexia. In RA patients, they attenuate the hepatic acute phase response and, importantly, improve patients quality of life.\(^{[45,46]}\) They have also been shown recently to prevent worsening of the disease and restore fat free mass.\(^{[47]}\) These drugs are now used to treat many thousands of patients and have been shown to be effective at blocking TNF-\(\alpha\), but are not effective in treating cancer-induced cachexia.\(^{[42,44]}\) The feature common to all of these diseases is chronic inflammation due to exaggerated production of pro-inflammatory cytokines. Etanercept has showed some promising results in improving fatigue in a small cohort of cancer patients.\(^{[48]}\) A phase I/II study was conducted on pancreatic cancer patients comparing etanercept and gemcitabine with gemcitabine alone. A small increase in progression free survival was seen associated with higher plasma IL-10 levels, but there was no significant improvement in 6 month progression-free survival compared with gemcitabine alone.\(^{[49]}\) A placebo-controlled double-blind trial was also undertaken in 63 patients with incurable malignancy and weight loss of > 2.27 kg over 2 months or daily intake of < 20 calories/kg body weight. Weight gain was found to be minimal in both arms with comparable survival times. Treatment was associated with higher neurotoxicity.\(^{[50]}\) In this trial, therefore, etanercept was not effective in the treatment of cachexia in patients with advanced disease.

Infliximab has been used in a phase II placebo controlled randomised study in patients with stage II-IV pancreatic cancer.\(^{[51]}\) Patients were given either 3 mg/kg or 5 mg/kg infliximab with gemcitabine or placebo with gemcitabine. The mean change in lean body mass was + 0.4 kg for those on placebo, + 0.3 kg for those receiving 3 mg/kg of infliximab, and + 1.7 kg for those receiving 5 mg/kg of infliximab. No statistically significant differences were seen, however.\(^{[51]}\)

Another agent with anti-inflammatory activity is OHR/AVR118, a broad-spectrum peptide-nucleic acid immune modulator that targets both TNF-\(\alpha\) and IL-6.\(^{[52]}\) A phase II study involving patients with advanced cancer and cachexia showed an improvement in anorexia, dyspepsia, strength, and depression.\(^{[53]}\)

**Anti-IFN-\(\gamma\) treatments**

Anti IFN-\(\gamma\) treatments have been effective in reverting cachexia in the LLC mouse model.\(^{[54]}\) There have been no trials undertaken in cancer patients, mainly due to the fact that this type of therapy requires a dose to completely block the action of IFN-\(\gamma\), and at present, such a treatment programme would be very expensive. The only trial conducted in patients with cachexia due to sepsis showed no benefit.\(^{[55]}\)
IL-1/6 inhibitors

The IL-1 pathway has been previously targeted in humans with the recombinant human IL-1 receptor antagonist Anakinra and the neutralising monoclonal anti-IL-1 antibody Canakinumab. Anakinra, as previously discussed, has had success in rheumatoid patients but has yet to be trialled in patients with cancer[65]. However, a more specific IL-1α human monoclonal antibody, MABp1, has shown promising results in cancer. An initial dose escalation and expansion study was designed using MABp1[73]. The first dose escalation study was performed in patients with refractory cancer to assess its safety and tolerability. It identified an optimal intravenous dose which was then used in the following phase II study of forty-two patients[73]. Median plasma IL-6 concentrations decreased from baseline to week 8 (\( P = 0.08 \)). Of those 30 patients who had an assessment of body composition, lean mass increased significantly by 1.02 ± 2.24 kg (\( P = 0.02 \))[73]. It was then compared to megestrol acetate in patients with advanced colorectal cancer and > 5% weight loss. Those in the MABp1 treatment arm showed a trend towards increased survival[74]. A placebo-controlled, double blind phase III study in 333 patients with advanced colorectal cancer was then undertaken which resulted in increased lean body mass as well as symptom relief (pain, anorexia, fatigue)[75].

IP1510 is a synthetic peptide IL-1 receptor antagonist. Pre-clinical studies found it to have low toxicity, and to be a potential effective treatment for cachexia. It was then trialled in advanced gynaecological cancer patients where it was well tolerated, and it significantly improved patient anorexia, depression and physical performance. Weight stabilisation or gain was seen in 17 of the 26 enrolled patients[76]. Interpretation of the current data is limited because the study was neither randomised nor controlled. However, further larger trials are to be initiated targeting IL1 in cancer cachexia[74].

Studies involving IL-6 antibodies have been undertaken in patients with advanced non-small cell lung cancer. The humanised monoclonal IL-6 antibody Clazakizumab [ALD518] has shown beneficial results in increasing haemoglobin levels and preventing loss of lean body mass. Fatigue scores were also improved compared with controls[77]. There are, however, no phase III trials underway.

Immunotherapeutic agents continue to be a promising treatment for cancer cachexia and may be added to the multi-modal management approach for this complex syndrome.

Standard cancer immunotherapy

Anti-cancer immunotherapy including bermekimab above has been shown to improve outcomes in a range of tumour types, including melanoma, lung and bladder cancers, many of which respond poorly to traditional agents. Some of these therapies are, however, poorly understood. Patients with cancer cachexia have been shown to respond poorly to some immunotherapies such as immune check point inhibitor therapy, likely due to elevated clearance or the establishment of primary resistance[78]. In two large clinical trials involving patients with melanoma and non-small cell lung cancer, there was a paradoxical association between plasma clearance of Pembrolizumab [a programmed cell death protein inhibitor (PD-1)] and poor overall survival. Those patients who responded poorly were noted to have reduced body weight and low albumin, suggesting that the presence of cachexia rendered these patients unable to respond to Pembrolizumab[78]. The hypoalbuminaemia was hypothesised to explain the elevated plasma clearance, and therefore the dose was increased in these patients to counteract this apparent resistance, but it did not result in improved outcomes. Studies in lung cancer patients treated with immunotherapy have shown that decreases in pre-treatment BMI, weight loss and high neutrophil:lymphocyte ratio were associated with significantly shorter progression-free survival[79]. However, other studies in lung cancer patients have also shown that two thirds of those receiving PD-1 and PD-L1 immune check point inhibitors experienced stability or an increase in their skeletal muscle index[80]. Thus, although at first glance immunotherapy would seem to be a natural antidote to cancer cachexia, it is difficult to unravel the clinical impact of immunotherapy from the known adverse outcomes of any cancer patients with poor nutritional status.
These studies therefore raise the possibility that immunotherapies could represent effective anti-cachexia agents but that synchronous multimodal and nutritional anti-cancer treatments may be required to establish or enhance their overall effectiveness.

A key consideration in using immunotherapy may be the inflammatory status of the host. It has been demonstrated that the host inflammatory status influences the efficacy of therapy with inflamed patients most likely to benefit from therapies with an anti-inflammatory mode of action\cite{81}. Similar to the call to “stage the tumor, stage the host”\cite{82} it is now key that treatment stratification is based on the inflammatory status of the patient and this is now being used as a mandatory measure in clinical trials in some tumour groups\cite{83}. It is clear that whilst immunotherapies as a treatment for cancer cachexia, there is a necessity to ensure patients who receive these are those who are most likely to benefit.

**CONCLUSION**

The pathogenesis of cancer cachexia is highly dependent on the patient’s immune response. The interplay between inflammatory cytokines (such as TNF-α, IFNγ and interleukins) and pro-cachectic factors contributes to the complex aetiology. These cytokines are produced by the host in response to the tumour, as well as by the tumour itself. Many treatments have tried to regulate the immune response in cachexia but have largely been unsuccessful, perhaps in part due to the multifactorial nature of cachexia, and the observed heterogeneity of patient factors. Large-scale clinical studies are needed to prove whether neutralisation of deleterious cytokines or direct receptor antagonism in combinatorial treatment regimens is an effective therapeutic approach to improve patient outcomes or to reverse muscle loss in cancer cachexia.

**DECLARATIONS**

**Authors’ contributions**

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Critically revised the manuscript and gave final approval for the version to be published: Laird BJA, Skipworth RJE

**Availability of data and materials**

Not applicable.

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68. Sproston NR, Ashworth J. Role of C-reactive protein at sites of inflammation and infection. Front Immunol 2018;9:754.
78. Hong D, Hui D, Bruera E, Janku F, Naing A, et al. MABp1, a first-in-class true human antibody targeting interleukin-1α in refractory